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Concomitant exercise training attenuates the cardioprotective effects of pharmacological therapy in a murine model of acute infectious myocarditis

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ABSTRACT

When administered alone, preinfection exercise training and benznidazole-based chemotherapy induce cardioprotection in Chagas disease. However, the effect of concomitant exercise and benznidazole treatment is unknown. We investigated whether exercise and specific chemotherapy could interact to modulate parasitemia, inflammation, redox status and heart damage in a murine model of *T. cruzi* infection. Wistar rats were randomized into an uninfected control group (CNT) and four groups infected with *T. cruzi*: sedentary untreated (SUN) and treated (STR), and trained untreated (TUN) and treated (TTR). Running training was administered 5 days/week for 4 weeks. Treated animals concomitantly received 100 mg/kg/day benznidazole. Heart inflammation and reactive damage were not detected in CNT animals. Compared to SUN, TUN animals presented increased levels of parasitemia, myocarditis, nitric oxide, hydrogen peroxide, protein carbonyl, malondialdehyde, cytokines (IFN-γ, TNF-α, IL-4, IL-6, IL-10 and IL-17), catalase, superoxide dismutase and glutathione reductase activity, as well as reduced heart non-protein antioxidant levels ($P < 0.05$). TTR animals exhibited higher levels of parasitemia, myocarditis, hydrogen peroxide, malondialdehyde, IFN-γ, TNF-α and IL-6 than STR animals ($P < 0.05$), which showed the lowest levels of all analyzed parameters compared to the other groups ($P < 0.05$). Our findings indicate that exercise aggravates acute infection. When concomitantly administered with benznidazole, exercise training impaired parasitic control and chemotherapy-induced cardioprotection in *T. cruzi*-infected rats. Considering that exercise training and *T. cruzi* infection constitute independent metabolic challenges, the negative effects of concomitant treatment are potentially related to the overlapping oxidative and immunoinflammatory demands of exercise and the infection itself.

1. Introduction

American trypanosomiasis or Chagas disease is a neglected tropical infection caused by the protozoan parasite *Trypanosoma cruzi*, which is endemic in Central and South America [1]. At least 8 million people are currently infected by *T. cruzi*, and 25 million people are at risk of infection worldwide, especially in areas with low socioeconomic development [2]. Chagas disease is responsible for > 10,000 deaths every year, primarily due to heart failure associated with chronic Chagas cardiomyopathy (CCC) [1,2]. At least 181,181 cases of Chagas disease were recently reported in Europe and 350,000 cases in North America [3,4]. However, the prevalence of Chagas disease in non-endemic areas may be much higher considering diagnostic limitations, underreporting of positive cases, and the increasing migratory flux of infected people [2,5].

The current etiological treatment for Chagas disease is based on benznidazole (Bz) and nifurtimox (NFx), two nitroheterocyclic drugs with high toxicity and limited efficacy in chronic infections [6–8]. About 30% of Chagasic patients develop CCC, the most severe and disabling manifestation of *T. cruzi* infection, which is associated with poor prognostic and a 2.48-times higher risk of death than non-infectious cardiomyopathies [5,9]. Complex and multifactorial processes are associated with the development of CCC, including parasite persistence, autonomic denervation, microvascular insufficiency, oxidative

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